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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,402	08/14/2001	Tsuneyuki Nagae	PO7336US00/LRP	8312

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,402	NAGAE ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 9/5/2006. Claim(s) 1-2 has been cancelled. Claim(s) 3-4 are pending. Claim(s) 3-4 has been amended. Claim(s) 3-4 are examined herein.

Applicant's arguments have been fully considered and found persuasive to withdraw the 103(a) rejection over Jenkins in view of Narciso only. The 103(a) rejection over Nyamekye in view of Narciso is maintained for reasons of record and repeated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3-4 rejected under 35 U.S.C. 103(a) as being unpatentable over Nyamekye et al (Circulation 1995; 91:417-425) in view of Narciso Jr, US Patent 5,298,018 and Aizaw et al US Patent 5,308,861.

The scope of the pending claims is essentially directed to a method of performing photodynamic therapy to reduce restenosis post an angioplasty procedure comprising administering Npe6 intravenously to a patient who has undergone an angioplasty procedure and subjecting the patient at a point of 0.5-6 hours after administration of Npe6 to a local irradiation of laser light of 664 nm wavelength at laser fluence of 1-10 J/cm2. Examiner adds that the delivery process instantly described in claim 3 is inherent to the PCTA procedure and those described by the cited prior art.

For example, Narciso teaches that photodynamic therapy during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the use of a photodynamic agent can be during, before or after a PCTA procedure (see col 2, lines 6-65). Narciso also suggests Npe6 to be a suitable photosensitizer for such treatment (see col 7, table 1, under class Phorobides). Since Narciso teaches the use of photodynamic therapy during a PCTA procedure, all method steps of the instant claims are also inherently disclosed.

Nyamekye teaches methods of administering photodynamic therapy to a mammal for inhibiting the development of intimal hyperplasia (restenosis) caused by a vascular intervention procedure such as balloon angioplasty (see abstract; pages 3-5). Nyamekye clearly teaches inhibiting restenosis in vessels of rats that have undergone a

balloon angioplasty and have experienced stretch injury of arorta. (sees page 8-9). Such teaching meets the instant limitation of suppressing thickening of vascular intima of blood vessels.

Nyamekeye uses 5-amiono-levulinic acid as the photosensitizer and applies a laser radiation of about 50 J/cm2 at 630 nm wavelength for a period of 30-90 minutes after administration of the photosensitizer (see page 3-5, under the heading "methods and material"). Nyamekyes administers his photodynamic methodology to rats after they have undergone an angioplasty procedure. Nyamekyes suggests photodynamic therapy given at suitable time after angioplasty will eliminate the expected restenosis post an angioplasty procedure (see page 13, last para). Nyamekye fails to explicitly teach the use of mono-L-aspartylch!orin e6 at a laser wavelength of 667 nm and a laser density of 1-10 J/cm2.

Narciso teaches that photodynamic theapy is also effective during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the use of a photodynamic agent can be during, before or after a PCTA procedure (see col 2, lines 20-35). Narciso also suggests Npe6 to be a suitable photosensitizer for such treatment (see col 7, table 1, under class Phorobides). Narciso teaches the activation wavelength of Npe6 to be about 660nm and describes suitable dosing. (see table 1). Narciso uses a light dose of 20J/cm2 (see col 8, lines 63-69; col 9, lines 19-34)_ Narciso teaches that the timing of light delivery following sensitization is about 32 hours and that determination of such parameter is a function of the pharmacokinetics of individual photosensitizers (see col 9,

lines 1-55). Since Narcisco teaches the use of photodynamic therapy during a PCTA procedure, all method steps of the instant claims are also inherently disclosed.

Aizawa is merely used to show that the local administration of Npe6 during an intravascular catherization procedure is well described in the art for its therapeutic effects (see col 21, line 60-col 26, line 20). Aizawa also teaches the same doses of Npe6 to produce photosensitizing effects. Aizawa fails to specifically describe the same method during a Percutaneous Transuluminal Coronary Angioplasty procedure (PCTA).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to substitute the ALA of Nyamekye with another photosensitizer such as Npe6 of Narciso and Aizawa and further improve the clinical outcome and prognosis of patients who undergo angioplasty procedures of Narciso or Nyamekye. One of ordinary skill in the art would have been motivated to use Npe6 in place of ALA, because as suggested by all cited references any suitable photosensitizer would have provided the same clinical results and are viewed to be art recognized functional equivalents in preventing restenosis secondary to an angioplasty procedure.

Finally, optimizing the laser wavelengths and density is a matter of routine experimentation and as described by Narciso a function of individual sensitizers.

Response to Arguments

Applicant argues that the present invention administers the photosensitive compound a single time, whereas Narciso discloses re-administration for 5 to 18 days. This is not persuasive because the present claims use "comprising," which is open claim language. Therefore, multiple or repeated steps read on the claimed invention.

Applicant argues that Narciso fails to teach inflating a catheter balloon at the prior angioplasty-dilated site during PDT to exert an outward force or pressure on the blood vessel. This is not persuasive because this limitation is inherent to the PDT procedure, which is known to one of ordinary skill in the art. Nonetheless, Narciso clearly disclose the use of photodynamic therapy during a PCTA procedure. Therefore, the use of a balloon catheter is inherent.

Applicant argues that Narciso teaches away from using a balloon catheter because gross damage can be done to the intimal surface of the blood vessel, which is also accompanied by rupture of the internal elastic lamina, disruption of the arterial wall and atheromatous plaque, as well as separation of the blood vessel tissue layers. Again, Narciso clearly disclose the use of photodynamic therapy during a PCTA procedure, which utilizes a balloon catheter. The referenced text is in the background section of the patent, where it is merely discussing some of the treatments for atherosclerosis, including PCTA risks and complications. Nowhere does it suggest that because of these risks, the present invention should not be practiced.

Applicant argues that Narciso teaches blocking the growth factor of SMC cells and treating arteriosclerotic lesions and plaque, whereas the present invention is directed to a method of preventing restenosis.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Nyamekye

clearly discloses a method of inhibiting the development of intimal hyperplasia or restenosis.

Applicant argues that the method disclosed in Narciso is distinguishable from the claimed invention because substantially less power, 1 to 10 J/cm^2, is used. This is not persuasive because Narciso uses a dose of 20 J/cm^2. Therefore, it is obvious to optimize the dosage when the general range is disclosed.

Generally, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

Applicant argues unexpected results from using a lower laser fluence to inhibit restenosis with no or few side effects.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side

comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

The Nagae declaration is not persuasive because it does not present a side-by-side comparison with the closest prior art in support of nonobviousness. Applicant is reminded that Narciso uses a light dose of 20 J/cm^2. Furthermore, there is no comparison with the closest prior art of the disclosed additional advantage of increasing the cross-sectional area of the vascular lumen.

Applicant argues that Narciso fails to teach or suggest a photodynamic therapy during PTCA procedure. Narciso clearly disclose using photodynamic therapy as an adjunctive therapy to PTCA. Applicant also argues that Narciso fails to teach using a photodynamic agent, but then admits on the record that Narciso uses Npe6 as a photosensitizer. For the record, Narciso clearly discloses Npe6 to be a suitable photosensitizer for such treatment (col. 7, table 1, under class Phorobides).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

S. Wang

SHENGJUN WANG
PRIMARY EXAMINER